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Therapeutic potential of long-acting opioids and opioid antagonists for SARS CoV-2 infection

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Editor – Aware of few reports of COVID-19 in patients undergoing opioid substitution treatment, we proposed that OST may have a protective effect on clinical manifestations of COVID-19[1] based on a publication proposing an interaction between opioids and SARS-CoV-2 pathology.[1a] We have not observed significant clusters of COVID-19 in the cohort of opioid substitution-treated patients, including attendees at our centre.[2] Establishing incidence of COVID-19 in people who use drugs is confounded by the tendency of many authors to aggregate all people who use drugs together although effects of individual drugs on immune function and viral infection differ.[3-4] Recent UK and US studies indicate a low incidence of COVID-19 in people who use drugs including, but not confined to, patients treated with opioid substitution treatment.[5-7] A US retrospective study concluded that patients with recent opioid use disorder were at higher risk for COVID-19 and that methadone, buprenorphine and naltrexone did not alter that risk.[8] However, detailed examination of this study does not provide strong evidence for this. The study was based on a small SARS-CoV-2-positive population, i.e. 210 (0.04%) of 471,520 patients with lifetime opioid use disorder and 90 (0.21%) of 43,160 patients with recent opioid use disorder. The majority had multiple co-morbidities and a third of those with lifetime opioid use disorder were over 65 yr of age. The opioid used was not stated, and patients with opioid use disorder who tested negative or were asymptomatic for COVID-19 were excluded as were those dispensed methadone in methadone clinics.

By contrast, the unexpectedly low incidence in opioid substitution-treated patients we reported previously continues to be maintained.[1] In July–October 2020 we conducted a seroprevalence study on 103 patients on opioid substitution treatment which showed that the majority of patient samples (100; 97%) tested were negative for the presence of antibodies to SARS-CoV-2.[2] Low incidence continued throughout the third wave of this pandemic when

case numbers peaked in Ireland with the more transmissible B.1.1.7 variant of the virus dominating. Data reported to WHO by Irish Health Protection Surveillance Centre (HPSC) for weeks 48 in 2020 to week 18 in 2021 encompassing the third wave of COVID-19 in Ireland reported over 180,000 cases of COVID-19, representing approximately 3.6% of the Irish population.[9] In this period the HPSC reported just 60 cases in "addiction settings" with hospitalisations and deaths (if any) in this group under the minimum threshold number for reporting.[10] HPSC indicated that 13 of these 60 cases self-reported as healthcare workers (HPSC, personal communication) inferring that there were 47 cases in the ~11,200 opioid substitution treatment population in Ireland (0.42 %), considerably lower than the general population (3.6%). This number also includes residential settings such as alcohol treatment /detoxification centres, where patients are not on opioid substitution treatment and may still include staff not identified as healthcare workers, so the cases in the opioid substitution treatment population is probably even lower than 47.

Consideration of possible mechanisms to explain a low incidence of disease in opioid substitution treatment patients raises the possibility that specific opioids interfere with the pathogenesis of SARS-CoV2, thereby affecting clinical manifestation of COVID-19 in the host. Review of immunomodulatory properties of opioids suggests that different opioids have a varied impact on immunity.[3] We have considered the widespread and varied systemic effects of opioids and opioid antagonists, their ability to stabilise cell redox balance and their antitussive properties which could attenuate respiratory symptoms in COVID-19 patients, (dyspnoea and cough), suggesting the possibility of a protective effect of opioid substitution treatment medications on clinical manifestations of SARS-CoV-2 infection.[1] The restorative effect of methadone on cellular immunity in injected drug use has been observed.[11] The therapeutic possibility for opioids in the treatment of COVID-19 has been identified including tramadol, given its anti-inflammatory, antioxidant, analgesic and antitussive effects.[12-13] Inhibition of the interaction of SARS-CoV-2 with ACE-2 by morphine and codeine has been identified as a therapeutic strategy for COVID-19.[14] Other *in vitro* studies included naloxone and naltrexone among drugs that could be repurposed for treatment of COVID-19.[15] Moreover, *in vitro,* naltrexone suppressed production of pro-inflammatory cytokines, and in docking simulation studies disrupted interaction between ACE-2 and the receptor binding domain of the SARS-CoV-2 virus spike protein, leading to a proposal to repurpose low dose naltrexone to treat patients with COVID-19.[16]

Our hypothesis is that the interaction of long-acting opioids or opioid antagonists with the ACE-2 receptor, considered the main route of viral entry into the host cell, mitigates the effects of COVID-19.[17] We also suggest that these drugs bind to toll-like receptor 4 (TLR4), a trans-membrane protein critical in the initiation of the innate immune response to pathogens also implicated in the pro-inflammatory response.[18-19] TLR4 recognises viral and bacterial molecular patterns and components of damaged cells, and its over-stimulation can lead to an aberrant inflammatory response implicating it in initiation and progression of various diseases.[18] Pro-inflammatory effects of opioids mediated by TLR4 have been studied providing evidence that opioid antagonists (naloxone and naltrexone) oppose these pro-inflammatory effects in a non-stereoselective manner.[20] Some reject the evidence of interaction between TLR4 and opioids suggesting opioids are exclusively immune suppressive.[21] Others propose that opioids activate TLR4 in the central nervous system but inhibit TLR4 signalling in the peripheral immune system.[22] A role for TLR4 in treatment of COVID-19 by selective targeting of the TLR4-SARS CoV-2 spike protein interaction using competitive TLR4 antagonists is suggested by *in silico* studies.[23] A link between TLR4 signalling in host cells and SARS-CoV-2-mediated inflammation has been observed via viral spike protein binding to host TLR4, and a therapeutic strategy targeting TLR4 inhibition and ACE-2 activation has been suggested.[18-19, 24] Our suggestion is that there is interplay between opioids, ACE-2, TLR4 and SARS-CoV-2. A TLR4–opioid ligand interferes with SARS-CoV-2-TLR4-ACE-2 signalling (Table 1).

Considering the low incidence of COVID-19 in the population on opioid substitution treatment we suggest that the interaction of specific opioids or opioid antagonists with the immune system affects the pathogenesis of COVID-19, and that the protective mechanism is via the particular interaction of these drugs with ACE-2 and TLR4. While the hypothesis is speculative, if correct, long-acting opioids or opioid antagonists or related drugs have potential as therapies or adjunctive therapies for COVID-19. This hypothesis could be tested by (1) analysis of COVID-19 disease patterns in patients treated with opioid substitution treatment; (2) *in vitro* studies on the effects of these drugs on viral infectivity in culture and; (3) clinical trials. The safe non-addictive opioid antagonist naltrexone, in particular, or other related drugs that do not display receptor opioid agonist activity could be candidates as therapies for COVID-19. There are ongoing or planned trials of opioids and opioid antagonists (including naltrexone and tramadol) for treatment of COVID-19.[25]

Regardless of the effects of opioids on immune function, opioid substitution treatment is a key strategy in the management of patients with opioid use disorder, and WHO recommends that untreated opioid-dependent individuals be entered into treatment.[26] Interactions of long-acting opioids or opioid antagonists with pathogenic mechanisms of SARS-CoV-2, particularly effects on ACE-2 and TLR4 interaction with SARS-CoV-2, merit further investigation.

Declaration of interests

The authors declare that they have no conflicts of interest. All authors are employees of the Health Service Executive of Ireland

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	Table 1. Summary of evidence for the therapeutic potential of long-acting opioids and opioid antagonists in the treatment of SARS-CoV-2 infection by effects on ACE-2 and TLR-4 receptors.
1.	An unexpectedly low incidence of COVID-19 has been observed in patients treated for opioid dependency with the long-acting opioid drugs methadone and buprenorphine. [1-2, 7, 4-10]
2.	Opioids have drug-specific and varied systemic immunomodulatory effects that may influence the response to the virus. [3,4,11,13]
3.	Opioids have antitussive properties that could attenuate respiratory symptoms in COVID-19 patients such as shortness of breath and cough [1]
4.	Opioids and opioid antagonists interact with the ACE-2 trans-membrane protein, a molecule that is widely considered to be main host cell receptor for SARS-CoV-2 cell entry. [14,16-17]
5.	Opioids interact with the membrane receptor TLR4, a component of the innate immune system implicated in the pathogenesis of SARS-CoV-2. [18-20, 22]
6.	*In vitro* and *in silico* studies aimed at repurposing drugs for treatment of COVID-19 have identified that opioids have therapeutic potential. [14-16,23]
7.	The opioid drugs morphine, codeine, tramadol, and the opioid antagonist naltrexone have been proposed for the treatment of COVID-19.[3,12-14]
8.	There are ongoing trials of some opioids including naltrexone and tramadol for the treatment of COVID-19 (NCT04604704; NCT04604678; NCT04365985; NCT04454307).[25]
9.	A strategy of selective targeting of TLR4-SARS-CoV-2 spike protein interaction using competitive TLR4 antagonists as a way of treating COVID-19 has been proposed [23-24]
10.	A combination therapy of diminazene aceturate (an ACE-2 activator) and novel antagonist resatorvid (a TLR4 inhibitor) has been proposed as a promising therapy for effective treatment of COVID-19 [24]
11.	While it is recommended that untreated opioid-dependent individuals should be promptly entered into opioid substitution treatment[26], related drugs that do not activate opioid receptors such as opioid antagonists (e.g. naloxone) may offer safer treatment options as typical opioid side effects would not be a problem.